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Award Number: W81XWH-12-1-0598

TITLE: Smart Oxygen Monitors to Diagnose and Treat Cardiopulmonary Injuries

PRINCIPAL INVESTIGATOR: Michael Kinsky, MD

CONTRACTING ORGANIZATION: University of Texas Medical Branch at Galveston  
Galveston TX 77555

REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
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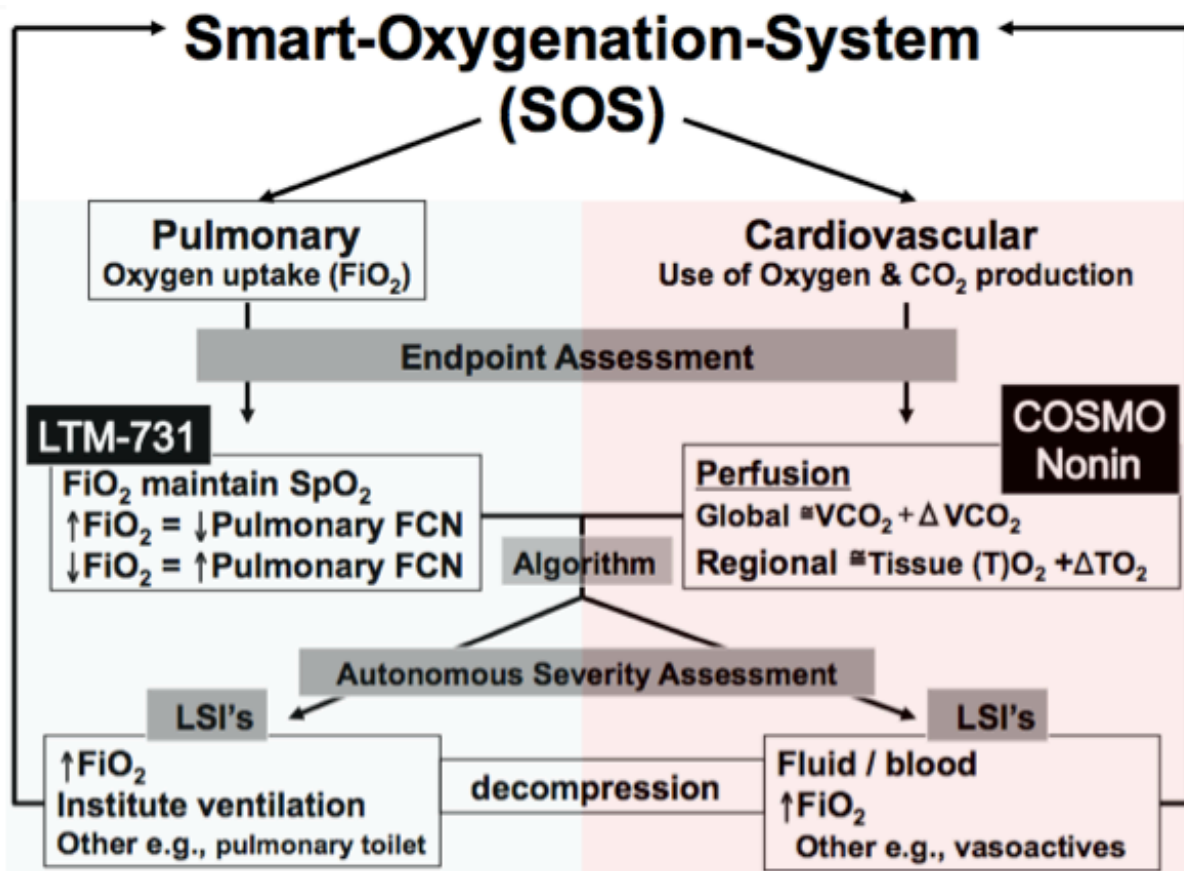
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1. REPORT DATE U&f à^ 2013		2. REPORT TYPE annual		3. DATES COVERED 30Sepà{ à^ 2012–29Sepà{ à^ 2013	
4. TITLE AND SUBTITLE  <b>Smart Oxygen Monitors to Diagnose and Treat Cardiopulmonary Injuries</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER . W81XWH-12-1-0598	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)  Michael Kinsky, MD  mkinsky@utmb.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  <b>University of Texas Medical Branch at Galveston</b>  <b>301 University BLVD Galveston TX 77555</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Resources and expertise needed to rapidly diagnose and initiate life saving interventions (LSI's) in soldiers suffering from chest trauma, hemorrhage and lung injury is a recognized gap for combat casualty care. Life threatening oxygenation deficits are characterized by the need for increased inhaled oxygen for pulmonary injury and perfusion for cardiovascular injury. Our group has developed autonomous closed loop systems that integrate technology with clinical expertise to optimize oxygenation, ventilation and fluid therapy. A fascinating element of autonomous systems is that they provide robust physiologic signals of clinical health due to feedback activity e.g., how active the autonomous controller is 'working'. Our project goal is to implement novel recognition systems (early warning alarms), which we term "smart-oxygenation-systems" (SOS), to treat patients with oxygenation deficits. Specifically, data from autonomous systems will be used to construct SOS that better detect oxygenation deficits that occur from hemorrhage and pulmonary/airway injury. SOS can be a standalone product or embedded into a variety of small emerging technologies. <i>We hypothesize that SOS will lead to earlier recognition and judicious use of LSI's.</i> We will first prototype and test these systems in animal experiments. Then, we will test our prototypes in patients. Two non overlapping, synergistic objectives will be performed.					
15. SUBJECT TERMS autonomous systems, closed loop controller, smart oxygenation systems, life-saving interventions					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	22	19b. TELEPHONE NUMBER (include area code)

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## Introduction:

Resources and expertise needed to rapidly diagnose and initiate lifesaving interventions (LSI's) in soldiers suffering from chest trauma and/or lung injury is a recognized gap for combat casualty care. Pulmonary injury is characterized by the need for increased inhaled oxygen (higher inspired oxygen percentage [FiO<sub>2</sub>]) to maintain oxygenation throughout the body. Deficits in perfusion occur when the cardiovascular system is compromised by hemorrhage, pneumothorax, and other forms of shock. The proposed project integrates non-invasive, commercial off the shelf (COTS) products with autonomous systems. Specifically, oxygenation data, which is continuously streamed and displayed in real-time, will be used to construct patient status and treatment algorithms. Our project goal is to implement novel recognition decision support systems with early warning alarms and display and/or initiate recommended therapies. These "smart-oxygenation-systems" (SOS) will identify oxygenation deficits in pulmonary function or circulation. A key component of SOS's are that they are built using a proven closed loop oxygen flow controller (CLC-FiO<sub>2</sub>). Additional information on global and regional oxygen deficits will be seamlessly adapted into these algorithms and displays using other small non-invasive COTS hardware such as COSMO capnography and Nonin Equanox.



Body:

## Quarter 1:

The PI, had several organizational meetings with all UTMB investigators and personnel as well as

several conference calls with outside investigators from ISR and hardware supplier of 731 – Impact. Specific roles and tasks have been outlined and agreed upon. Co-investigator, Rich Branson, came to UTMB from 01-28-2013 to 01-30-2013 to visit the PI and instruct the PI and his team on the 731 CLC-FiO2 algorithms and overall user function.

We began initial hardware testing for the COSMO [VCO2 as input] and Nonin [tissue O2 as input]. Specifically, the acquisition and capability of these non-invasive oxygenation surrogates to detect oxygen deficits during a slow hemorrhage in an anesthetized pig was tested. Data from these non-invasive monitors will be used to develop algorithms that detect cardiopulmonary oxygenation deficits.

Briefly, the pig was anesthetized, endotracheally intubated (ETT) and instrumented with arterial lines and a Swan-Ganz continuous cardiac output catheter for hemodynamic monitoring. The COSMO flow sensor was placed on the ETT and Nonin rSO2 sensors were placed on head [Brain rSO2] and thigh [muscle rSO2]. All data was captured in real-time and digitally stored using Powerlab software. At Time 0, a moderately sized [30 mL/kg] but slow [over 3 hr] hemorrhage was begun.

Figure 1:

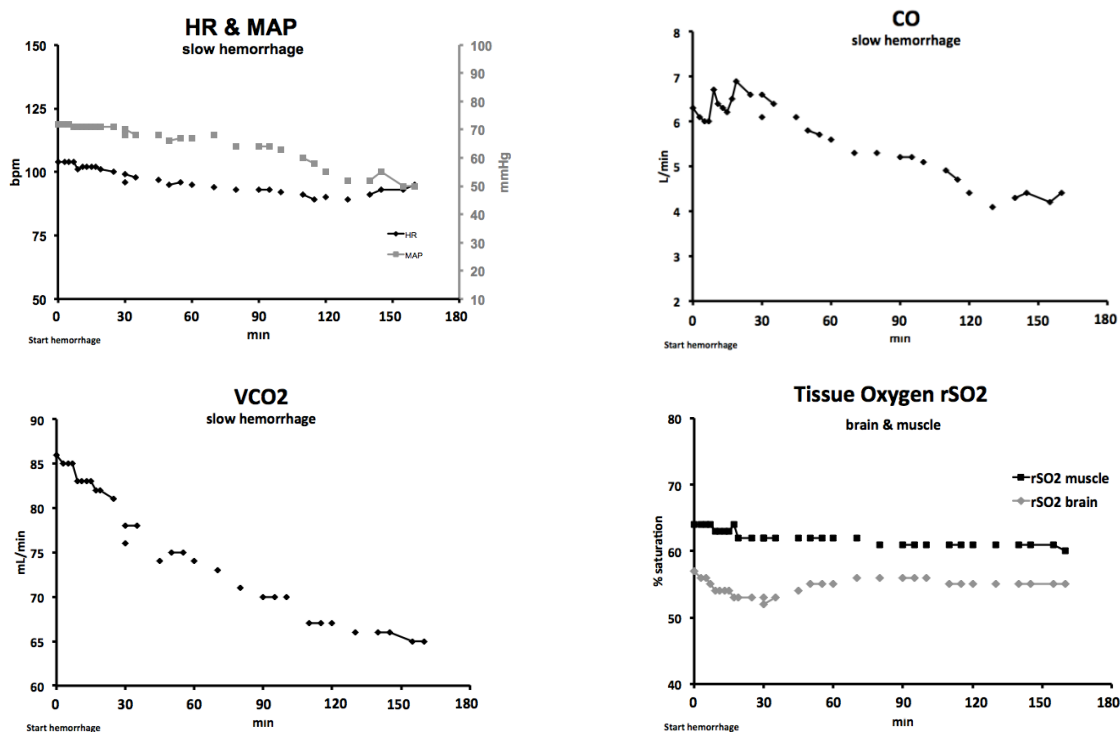


Figure 1. Time-course of a three-hour blood removal. Heart rate changed little and blood pressure was preserved or compensated during the first 10 mL/kg, but thereafter decreased proportionally. The decrease in cardiac output was directly related to blood removal. VCO2 was tightly proportional to hemorrhage and tissue oxygenation (rSO2) showed little change. The data suggests that VCO2 tightly correlates also with cardiac output [ $r^2=0.83$ ] and could be an excellent surrogate of oxygenation deficits.

## Quarter 2:

Task #1: Collect oxygenation data (FiO2 and SpO2) and other data in sheep after moderate and severe inhalation injury.

The response of CLC-FiO2 and SpO2 will be used to generate and tune the SOS to recognize developing pulmonary insufficiency. During this quarter, we collected data in conscious sheep subjected to lung injury through burn and smoke (n=4). Sheep were instrumented per protocol, and a pulse oximeter was placed. Oxygenation, ventilator and hemodynamic parameters were manually recorded during and after smoke inhalation. We had some difficulty obtaining a reliable SpO2 signal due to anatomic placement and movement of the sheep. We used the natural skin folds of the animal and blocked excess ambient light to get a better signal.

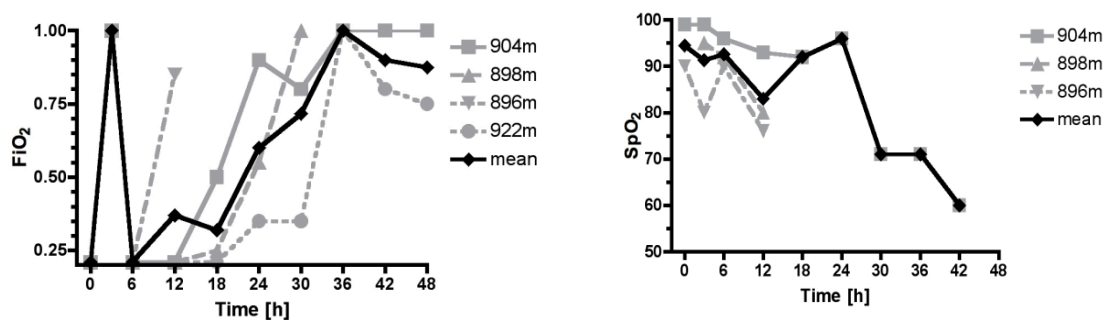


Figure 2: The data shows the indirect relationship between oxygen saturation (SpO2) and FiO2. As the severity of lung injury increases (low SpO2), the need for a greater FiO2 increases. Note sheep 896m and 898m did not survive the 48 hour time limit of the experiment with them dying at 18 hour and 36 hour respectively. There was a dramatic increase in FiO2 over that time period.

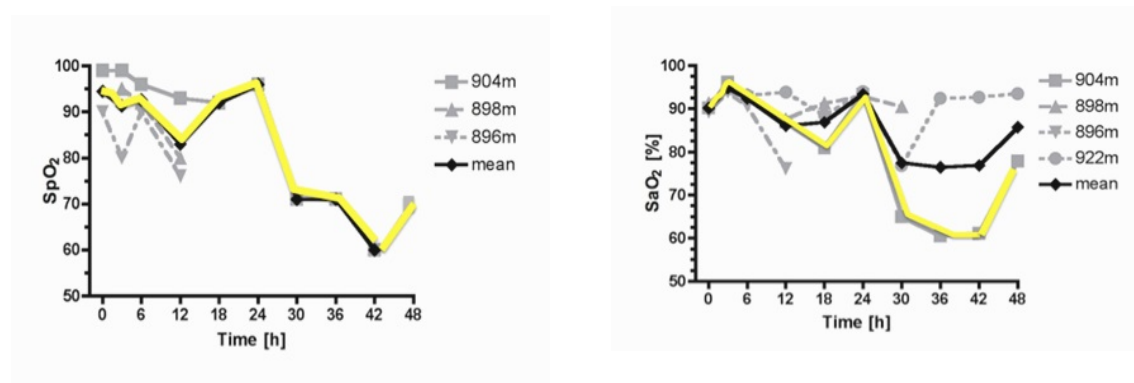
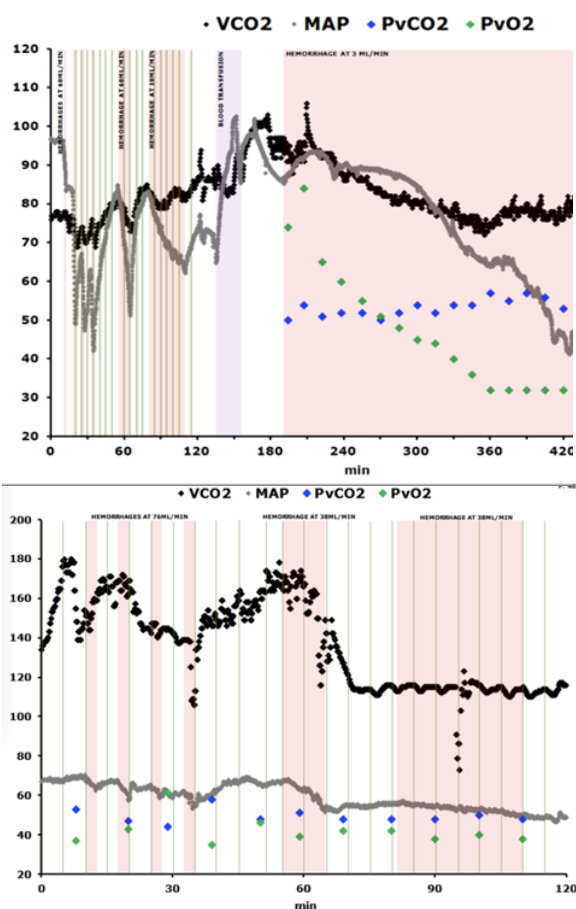


Figure 3: A representative experiment [yellow outline – experiment 904m] shows a close trend and values for SpO2 and SaO2. SaO2 is a direct measurement of oxygen saturation and can be monitored more accurately unlike SpO2 which can be affected by location of sensor, animal movement, and ambient light. While we will monitor SpO2 per protocol, SaO2 data can also be used in order to calculate corresponding SpO2 if it is unavailable.

Task #5: Collect FiO<sub>2</sub>, SpO<sub>2</sub>, ventilatory parameters, CO<sub>2</sub> production, hemodynamics, and indices of perfusion during hypovolemia and pulmonary injury.

Data from the CLC-FiO<sub>2</sub> with ventilator and perfusion indices will be used to construct a SOS to recognize cardiopulmonary insufficiency. Non-invasive perfusion indices [VCO<sub>2</sub> from Cosmo] are being compared to invasive metrics [arterial blood pressure, cardiac output and mixed venous oxygen] before, during, and after cardiovascular collapse. Isolating the perfusion deficits during hypovolemia itself or coupled with a concurrent lung injury is important. We recorded and analyzed high-resolution hemodynamic data, along with data from COSMO [VCO<sub>2</sub>] and other devices to determine if surrogate non-invasive oxygen consumption can detect perfusion and oxygenation deficits accurately.

In these experiments, pigs were anesthetized, endotracheally intubated (ETT) and instrumented with arterial lines and a Swan-Ganz cardiac output catheter for hemodynamic monitoring and mixed venous oxygenation. A COSMO flow sensor was placed on the ETT. All data was captured in real-time and digitally stored using Powerlab software. Various experimental hemorrhages (n=5) were performed. Experimental data was collected on VCO<sub>2</sub>, mean arterial pressure (MAP), and mixed venous oxygenation (PvO<sub>2</sub>).



The first experiment shows a series of small hemorrhages followed by resuscitation (T0 – T180). Then, at T-180 a slow, but large size (25 mL/kg) hemorrhage was initiated over a four hour time frame. Mean arterial pressure (MAP) showed a slight increase initially over the first hour, maintained the pressure over the next hour (T240 – T300) and then decreased dramatically. VCO<sub>2</sub> showed an increase similar to MAP in the first hour, decreased slowly thereafter and finally leveled off. Mixed venous oxygenation [PvO<sub>2</sub>] is the “gold standard” of global perfusion. The decrease in

PvO<sub>2</sub> is caused by the decrease of cardiac output (hemorrhage). The continual need of oxygen throughout the body increases the oxygen extraction out of the blood.

The second experiment represents several small hemorrhages and resuscitations. The total hemorrhage volume for this experiment was modest (10 mL/kg total). MAP showed very little change – a small increase during resuscitation. Incremental drops followed by increases in VCO<sub>2</sub> were observed during hemorrhage

Figure 4. oxygenation and perfusion data

and resuscitation. At T60, a slightly larger hemorrhage was induced and VCO<sub>2</sub> decreased. PvO<sub>2</sub> changed little during the small/modest hemorrhage.

To test the association between VCO<sub>2</sub> and cardiac output a regression analysis was performed. Data suggest that VCO<sub>2</sub> has a high correlation with cardiac output [ $r^2=0.62$ ] and overall perfusion. Cardiac output and VCO<sub>2</sub> data were obtained in 5 animals. Figure 5 shown below:

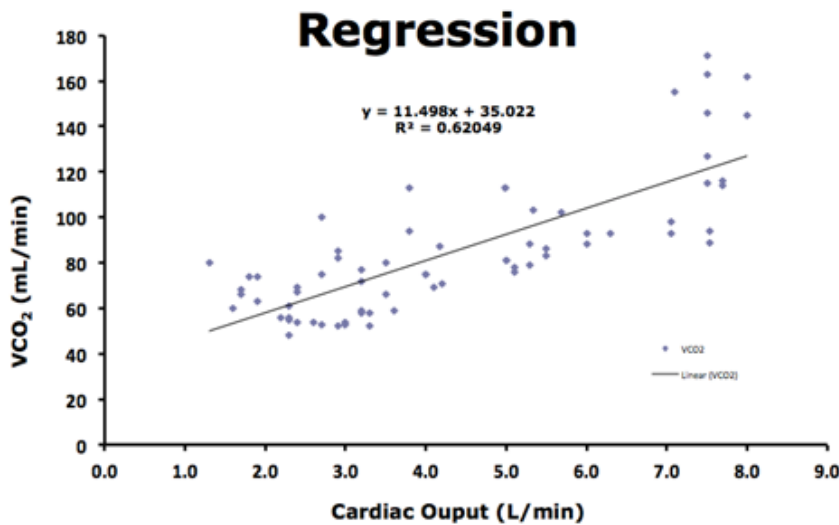


Figure 5. regression analysis comparing cardiac output to VCO<sub>2</sub>

VCO<sub>2</sub> data will be incorporated into the perfusion aspect of the SOS cardiopulmonary prototype. Multi-variable analysis will likely be used and data from these non-invasive monitors will be used to develop algorithms that detect cardiopulmonary oxygenation deficits. Our overall objectives will determine if these inputs can be used for to generate algorithms that can determine need of life saving interventions.

Issues:

- We began testing hardware [731 ventilator/ Cosmo and other devices that will be incorporated into our SOS algorithm and future prototype] and collecting data in two separate studies. Specifically, we have tested the performance of the 731 ventilator and activation of the closed loop control (CLC)-FiO<sub>2</sub> algorithm. While we have been able to demonstrate increases and decreases in FiO<sub>2</sub> based on altered SpO<sub>2</sub> [O<sub>2</sub> saturation via pleth signal], we have observed a prolonged response time to the CLC-FiO<sub>2</sub> algorithm activation. Further, the data stream protocol [software capture program] that communicates the digitally stored data on the ventilation parameters from the 731 lacks compatibility. To address these technical issues, we have contacted software engineers that have specific expertise with the 731 ventilator as well as Rich Branson [Co-I – 731



ventilator user who conducted this specific clinical trial] and Impact engineers. Progress has been made in understanding the time response and another data stream protocol is being tested. We have also ordered additional data connectors. Since we are only in our data capture portion of the study, we are manually recording SpO<sub>2</sub> and FiO<sub>2</sub> data.

- As discussed in Figure 3, we had difficulties establishing a reliable SpO<sub>2</sub> signal on the conscious sheep study and will continue to refine location and technique when attaching the sensor.

### **Quarter 3:**

The PI met with George Beck [VP Impact] and Rich Branson [Co-investigator and lead scientist that conducted previous CLC-FiO<sub>2</sub> studies using the 731 ventilator]. To handle this problem, a product design firm [Sparx], familiar with the 731, was located. Mr. Beck and Sparx provided assurances that download protocol problem would be resolved. The responsiveness of the CLC-FiO<sub>2</sub> based on SpO<sub>2</sub> and excess aberrant signals or noise, remains problematic [see 731 testing qtr 4]. We continue to work closely with engineers to reduce this problem. We have adapted the scope of our studies to include a decision support arm and directed a search for another ventilator with closed loop capability was needed and other options to accomplish our tasks.

Recently, our lab began using a new ventilator [Hamilton G5] for doing chronic large animal studies. Fortuitously, the G5 ventilator also has the ability to do CLC-FiO<sub>2</sub> [software package – called Intellivent]. Specifically, the upgraded software has an autonomous driver for performing closed loop adaptive support ventilation [ASV], PEEP and FiO<sub>2</sub>. Hamilton's R&D leadership have met and provided the PI and his team with several hours of in-service training for the G5 Intellivent. During this time, the PI attended an Intellivent workshop, consulted with Hamilton's R&D and owner, and submitted a purchase order to obtain the CLC-FiO<sub>2</sub> controller. There are other advantages to using Hamilton's G5 ventilator and the option for using Intellivent:

- 1) The ventilator is also a deployed system for the DOD,
- 2) Since we are now using the G5 as standard of care for our studies, it will allow for stronger scientific comparison testing
- 3) Hardware and other capabilities are similar to 731 with COSMO [VCO<sub>2</sub>]:
  - a. VCO<sub>2</sub> can be automatically measured
  - b. SpO<sub>2</sub> sensor can use Masimo pulse oximeter
- 4) The ventilator has adaptive support mode for autonomous ventilation and other decision support capabilities.

### **Task #1: Collect oxygenation data (FiO<sub>2</sub> and SpO<sub>2</sub>) and other data in sheep after moderate and severe inhalation injury.**

The pathophysiology demonstrates a predictable response for increasing oxygen requirements, need for ventilation and pulmonary toilet.

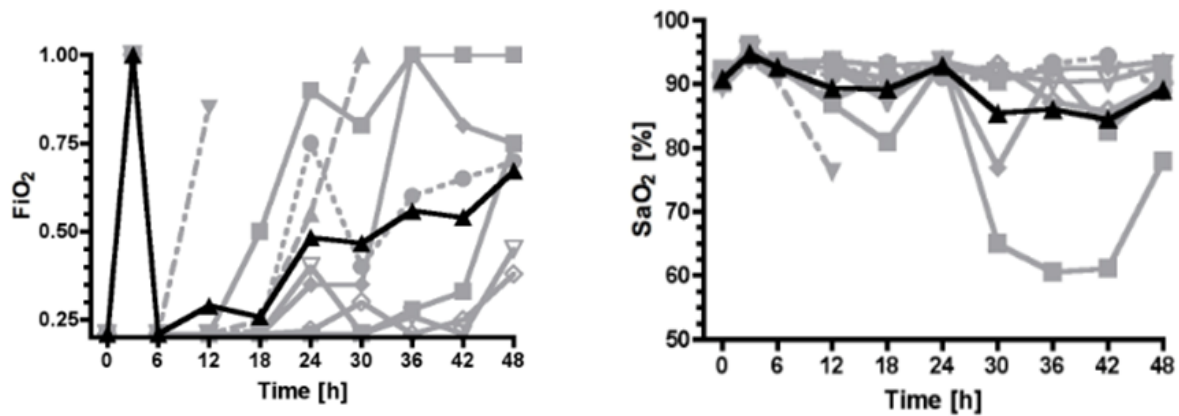


Figure 6.  $FiO_2$  and oxygen saturation.  $FiO_2$  increases after smoke & burn injury; while  $SaO_2$  decreases

Our goal was to collect  $FiO_2$  and  $SpO_2$  to determine the future timing for when interventions could be done (figure 6). We collected data in conscious sheep (n=8) subjected to lung injury [burn & smoke], which represents our Standard of Care (SOC). Oxygenation, ventilator, and hemodynamic parameters were manually recorded during and after smoke inhalation. The sheep were ventilated and provided oxygen from the onset of injury. Data, below, shows  $FiO_2$  continued to increase in order to maintain  $SaO_2$  /  $SpO_2$ .

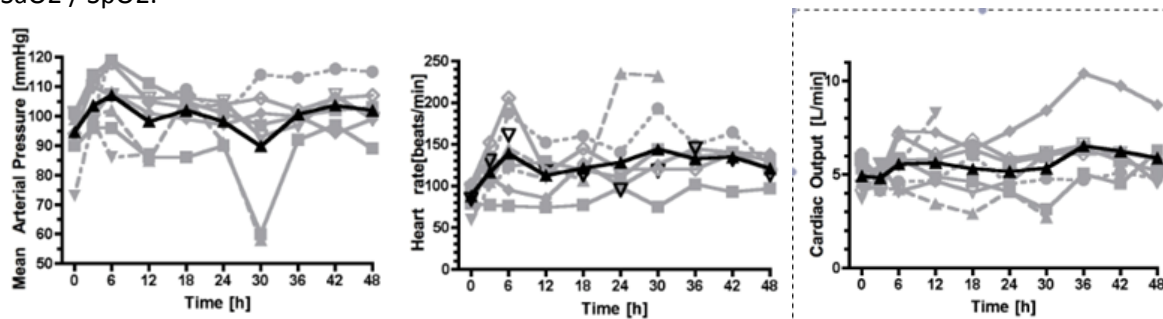


Figure 7. Hemodynamics after burn and smoke injury

Figure 7. Hemodynamic data showed that mean arterial blood pressure [MAP], overall, underwent small changes after burn and smoke injury. In some animals, there were pronounced effects on MAP. Cardiac output increased overtime and was higher at study end than at start, which occurs due to resuscitation of a 40% total body surface area burn. Heart rate underwent the most change in any hemodynamic variable.

### **Task #3: Test SOS vs Standard of Care (SOC) for determining LSI (need for ventilation and pulmonary toilet) after moderate and severe inhalation injury in sheep.**

The DS algorithm is a logical and incremental step before closed loop control. We have adapted our scope to include a DS scheme— in sheep after burn & smoke injury – to support oxygenation and ventilation. The decision support SOS algorithm uses SpO<sub>2</sub> to adjust FiO<sub>2</sub> and other parameters to advance ventilation and other LSI's [Task #3, n= 3 sheep]. Key differences were that spontaneous ventilation occurs from onset [which is closer to clinical practice], FiO<sub>2</sub> adjustments are made based on hourly SpO<sub>2</sub>/SaO<sub>2</sub> readings, advanced ventilation is done when FiO<sub>2</sub> reaches a threshold value of 0.6, and positive end-expiratory pressure (PEEP) would be used. All actions were performed on a G5 ventilator.

- Modes
  - 1st hr (T0-T1) – SIMV
  - After 1 hr, or when standing or fully awake switch to SPONT
  - ASV when FiO<sub>2</sub> >0.6, RR >30 or other clinical signs of distress
  - If ASV alarm occurs “unable to achieve minute ventilation” then CMV
- SaO<sub>2</sub>
  - not used - unless PaO<sub>2</sub> less than 65. Rare, but if does:
    - FiO<sub>2</sub> is immediately increased to 1.0 .
    - Note : "SaO<sub>2</sub> + aCOHb ≈ SpO<sub>2</sub>" Thus SpO<sub>2</sub> is endpoint
- FiO<sub>2</sub>
  - at T1 hr - switch FiO<sub>2</sub> from 1.0 to 0.4
  - if ≥ 0.6, start ASV mode
- FiO<sub>2</sub> Adjustments based on SpO<sub>2</sub> – adjust to achieve a SpO<sub>2</sub> = 95%
  - If SpO<sub>2</sub> ≥ 95, then lower FiO<sub>2</sub> by 5 points [or 0.05]
  - If SpO<sub>2</sub> < 95, then increase oxygen 5 points [or 0.05]
    - Example – If SpO<sub>2</sub> reads 90% and current FiO<sub>2</sub> is set at 0.4 then
      - Increase FiO<sub>2</sub> to 0.45 [or 45%]
    - Example – If SpO<sub>2</sub> reads 96%, and current FiO<sub>2</sub> is set at 0.55 then
      - decrease FiO<sub>2</sub> to 0.50 [or 50%]
- PEEP
  - Start at 5
  - If > 0.8, increase PEEP to 10
  - Once PEEP is increase to 10 do not decrease
- Pulmonary Toilet
  - When PEAK ≥ 30 or excessive secretions (or as needed; see example below)
  - turn FiO<sub>2</sub> to 1.0 during suctioning; then return to previous setting
- Hourly Readings
  - Read Masimo SpO<sub>2</sub>. Make sure reading is stable. [May need to wait 5-10 minutes].
  - Hourly readings can be adjusted to least interfere with concurrent runs – but w/in 20 min.
  - The goal is to continuously adjust FiO<sub>2</sub> at regular intervals 48 hrs post injury.

**DS versus SOC:** There is a very clear rapid increase in  $\text{FiO}_2$  between hours 18-24 after burn and smoke inhalation. This was the result of preceding hypoxemia. Episodic decreases in  $\text{SpO}_2$  occurred despite high  $\text{FiO}_2$  due to excess secretions/mucous plugs [figure 8]. The high peak pressure alerted the user to initiate pulmonary toilet. Using the decision support scheme, incremental changes to  $\text{FiO}_2$  resulted in tighter control of  $\text{SpO}_2$ . We envision that the CLC will allow tighter control and provide early warning alarms that the need of positive support ventilation and pulmonary toilet is needed in order to recognize and prevent drastic falls in oxygen saturation.

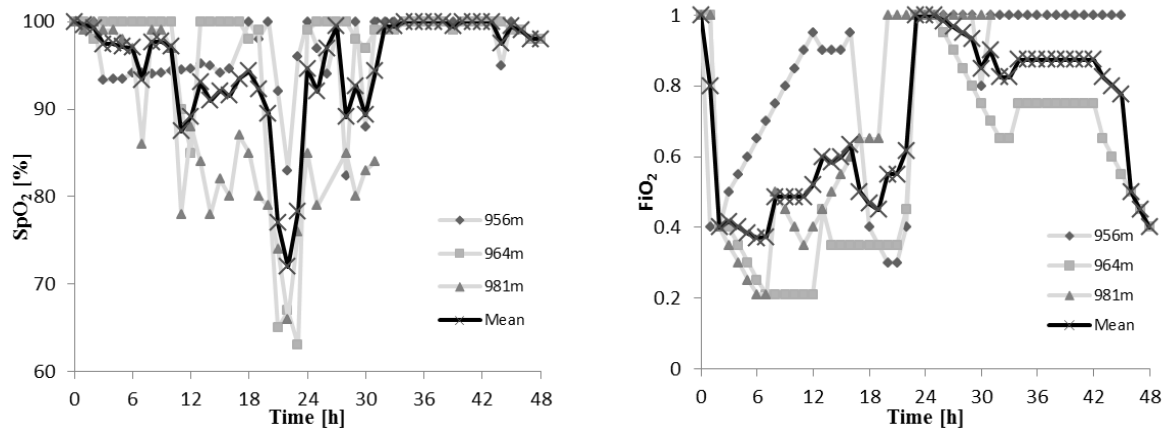


Figure 8.  $\text{SpO}_2$  and  $\text{FiO}_2$

Figures 9-23, compare standard of care {[SOC][n=8]} to decision support {DS [n=3]}: Mean  $\pm$  SEM are represented below.

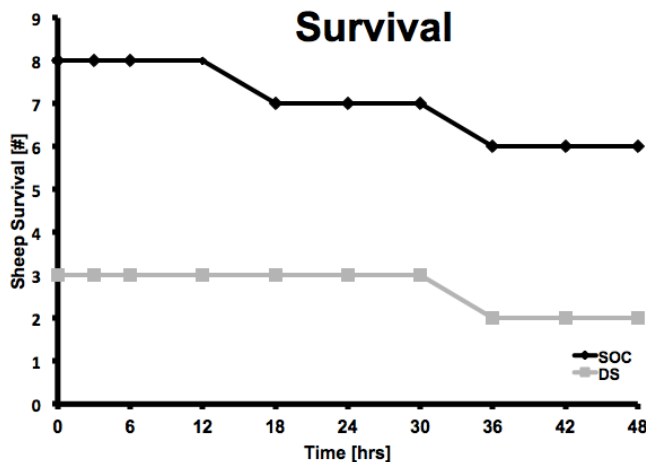


Figure 9. shows the survival of sheep using the "Standard of Care" (SOC) [n=8] method compared to "Decision Support" (DS) [n=3]. Two sheep in the SOC did not survive the 48 hour experiment. One died in our 18 and another in hour 36. In the DS group, one sheep died in hour 31.

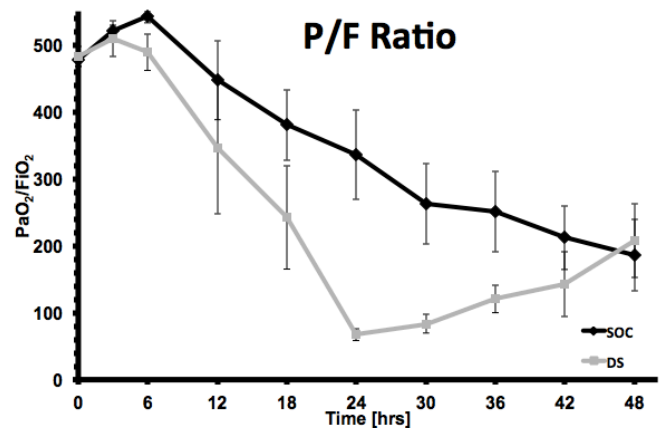


Figure 10. the ratio of  $\text{PaO}_2$  to % fractional inspired oxygen [P/F]/. Both groups show a decrease in P/F ratio over 48 hours and represent deteriorating lung function. The decision support group (DS) shows a more rapid decline from T6 – T24 while the SOC group shows a more steady decline after burn and smoke inhalation. At T48, the ratio is similar for both groups.

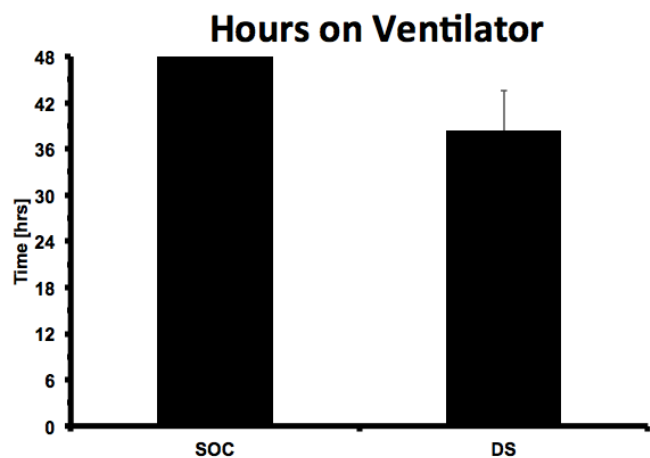


Figure 11. Mechanical ventilation in the decision support (DS) group was less. This is somewhat by design as SOC were ventilated at onset of 48 hour experiment.

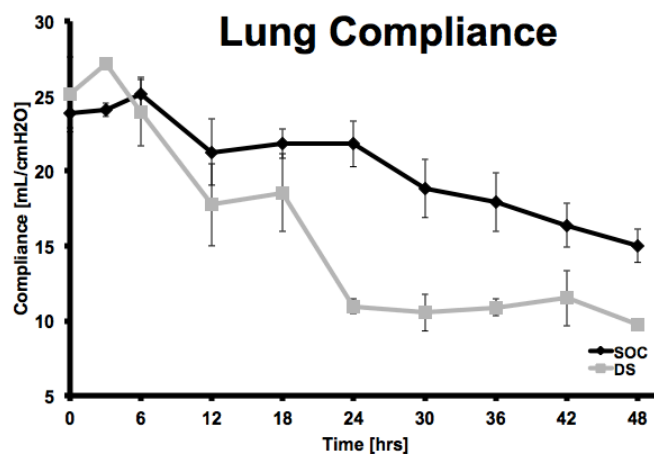


Figure 12. Pulmonary compliance falls over course of study. This represents the severity of injury due to burn and smoke inhalation. The DS group has a more significant decline in compliance than the SOC.

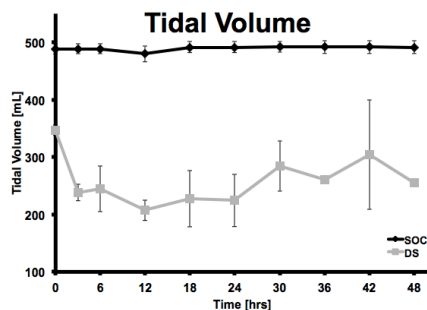


Figure 13. shows the variability in tidal volume during the study length. The "Standard of Care" used mechanical ventilation to keep a consistent tidal volume throughout the study. During the "Decision Support" study, sheep were allowed to breath spontaneously.

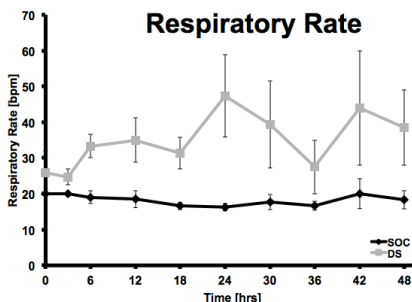


Figure 14. demonstrates the increase in the respiration rate during "Decision Support" as lung condition worsened. Dramatic increases were seen at T18 - T24 and T26 - T42. The "Standard of Care" used a fixed mechanical ventilation rate to control minute ventilation.

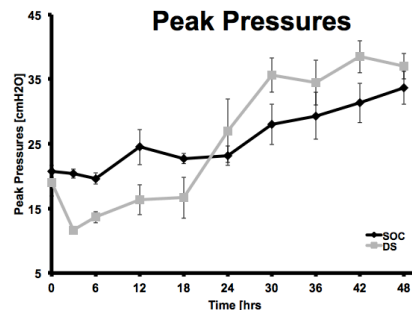


Figure 15. demonstrates the increasing trend of peak pressures in both SOC and DS groups. Each group shows a steady increase after T6 which corresponded to progressive deterioration of lung injury.

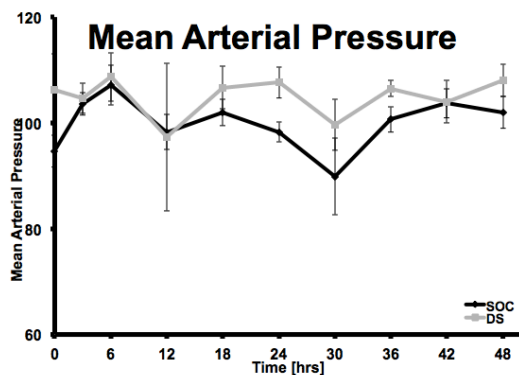


Figure 16. demonstrates the stability of mean arterial pressure of both groups throughout the experiment.

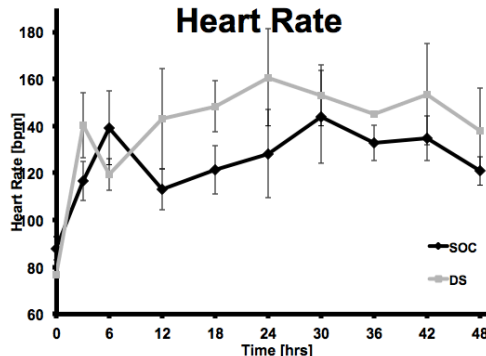


Figure 17. demonstrates a marked increase in heart rate initiation of burn and smoke inhalation, which remained elevated until the end of the experiment. Heart rate had the most change for hemodynamics.

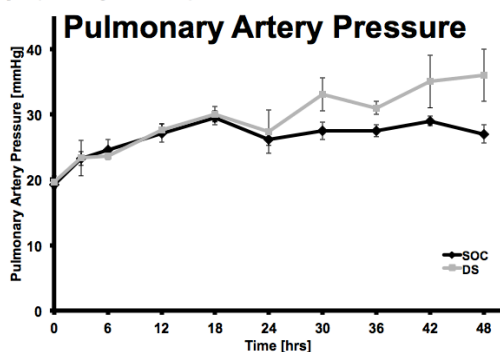


Figure 18. demonstrates the steady increase in pulmonary artery pressure. Both groups have similar trends and values over the entirety of the experiment.

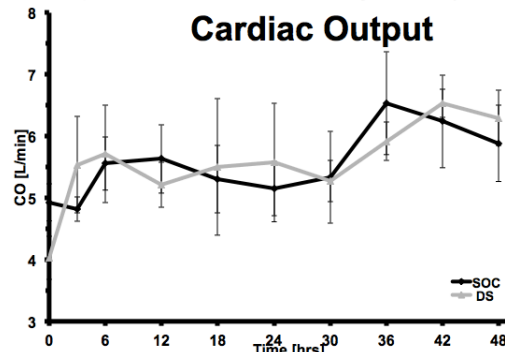


figure 19. shows cardiac output [CO]. After burn and smoke inhalation, both groups had a steady increase in CO.

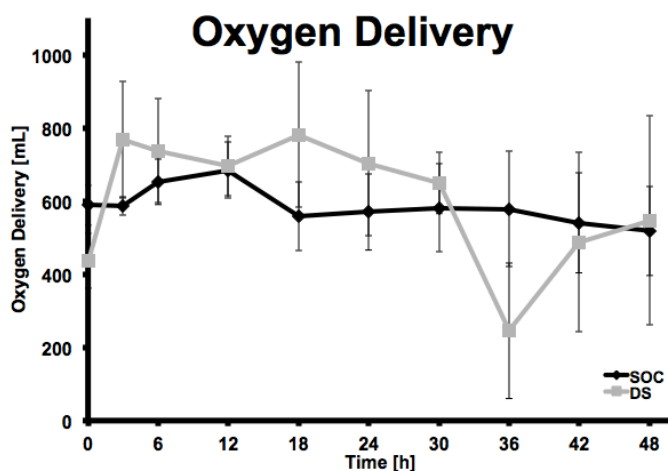


Figure 20 shows the amount of oxygen delivered [CO X Hb X SaO<sub>2</sub>] to the tissues. While the SOC group showed only a modest increase, the "Decision Support" group had a more dramatic increase from baseline.

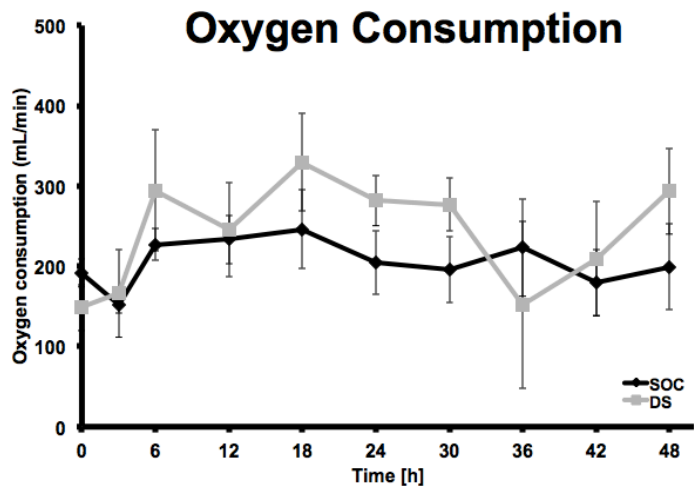


Figure 21. demonstrates the increase need of oxygen in the tissues based on extraction of oxygen using PA catheter. Both demonstrated an increase in consumption throughout the study.

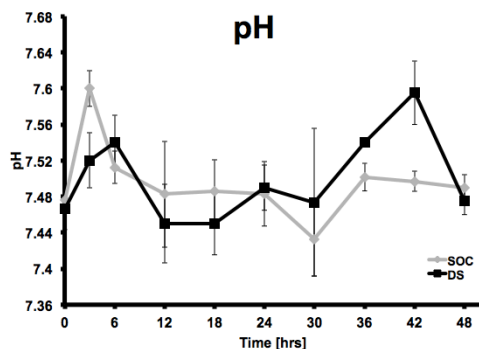


Figure 22. demonstrates an initial increase in pH both groups is shown during initiation of burn and smoke inhalation

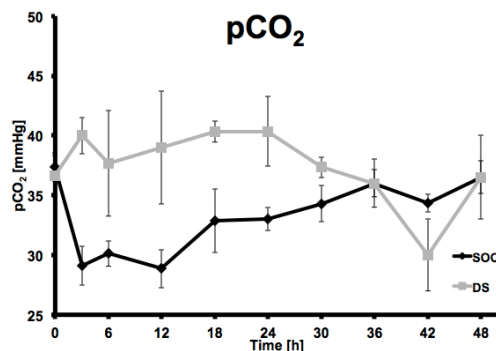
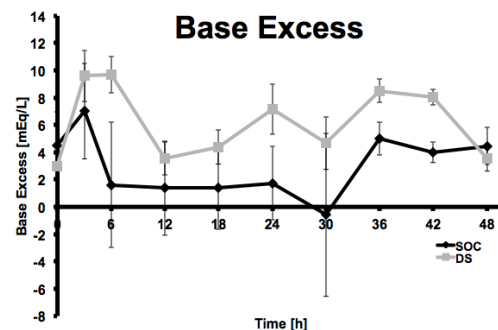


Figure 23. demonstrates the difference in the partial pressure of CO<sub>2</sub> of the SOC and DS groups. The pCO<sub>2</sub> was reduced in the SOC group, whereas closer to baseline in DS.



Figures 24 shows a trend towards reduction in SOC, however, BE was had high variability with an increase within the first 3 hours, that returned towards basal levels at study end.

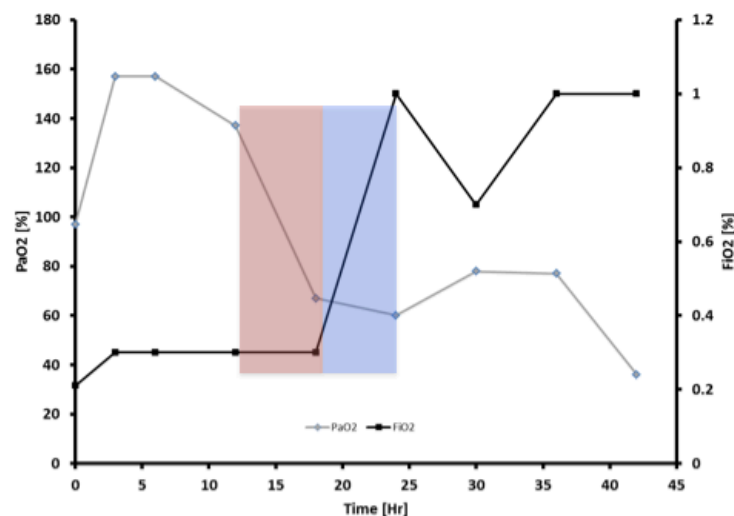
**DS Results summary:** Figures demonstrate the data that we are/will be capturing. Outcome data include survival, pulmonary function, hemodynamic endpoints and tissue oxygenation. The ventilation strategies differ. For SOC, ventilation is controlled from the onset of injury with a fixed tidal volume and respiratory rate. Interestingly, initiation of controlled ventilation might confer some protection [potentially less respiratory work]. However, by 48 hr, this effect was not apparent and the P/F for DS was increasing. It better remains to be determined if tighter control of oxygenation and ventilation will improve outcome. The DS group will be completed in next several months.

#### Quarter 4:

Recently, our lab began using a new ventilator [Hamilton G5] for doing chronic large animal studies. Fortuitously, the G5 ventilator also has the ability to do CLC-FiO<sub>2</sub> [software package – called Intellivent]. For redundancy purposes and market competition, we pursued another usability platform with a Closed-Loop-FiO<sub>2</sub> Controller [G5 Intellivent - Hamilton]. Specifically, the upgraded software has an autonomous driver for performing closed loop adaptive support ventilation [ASV], PEEP and FiO<sub>2</sub>. Hamilton's R&D leadership have met and provided the PI and his team with several hours of in-service training for the G5 Intellivent. Moving forward, we now have two different CLC-FiO<sub>2</sub> platforms [Impact 731 and Hamilton G5 Intellivent]. The PI has an excellent relationship and support from both industrial 'partners'. To our knowledge, we are the only group in the US using the G5 Intellivent. Most unique, we are the only group incorporating the CLC-FiO<sub>2</sub> signal [FiO<sub>2</sub> response rate] to develop software to detect the need for life saving interventions.

#### **Task #2: Develop SOS algorithm and prototype for pulmonary injury.**

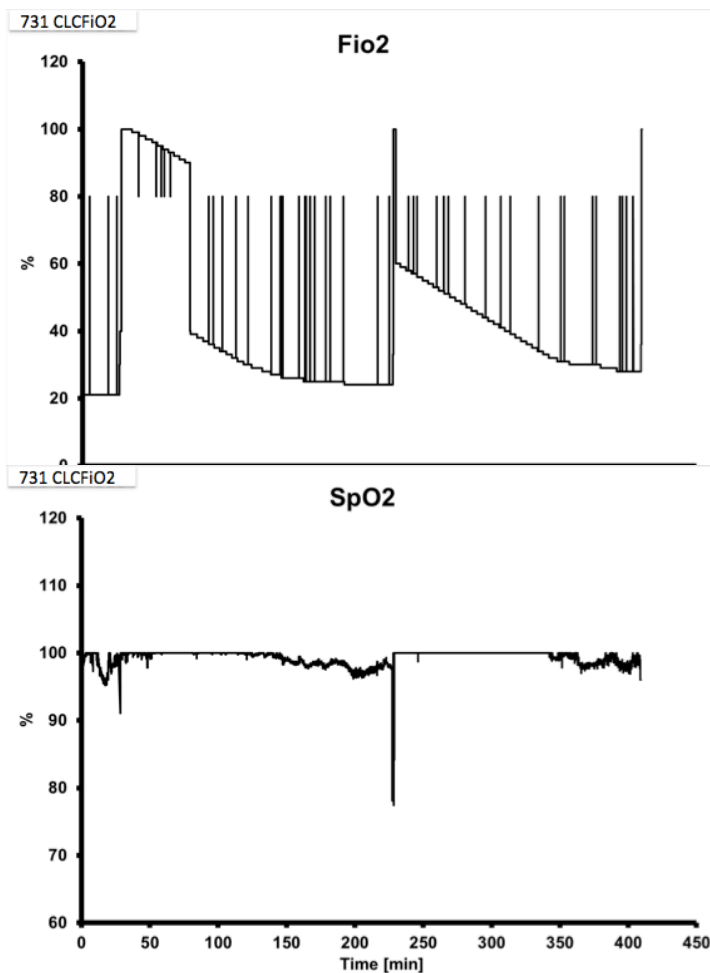
Oxygenation delay and need for early detection: Adjusting the FiO<sub>2</sub> based on preceding saturation or amount of blood oxygen leads to a significant time delay. Figure 25 shows a significant time delay [hours] between recognition and treatment. Patients could be administered excess O<sub>2</sub> from the onset, however, this leads to the concept of 'oxygen blindness'; whereupon higher levels of O<sub>2</sub> than needed are administered. This practice leads to sequelae of excess oxygen buildup. The use of close loop control FiO<sub>2</sub> reduces the time delay and excess O<sub>2</sub> and provides information on the patient's physiologic state.



**Figure 25 demonstrates retroactive changes in FiO<sub>2</sub> based on PaO<sub>2</sub>, standard management for pulmonary injury. At time zero [0 hr], pulmonary injury was induced by smoke insufflation. Sheep were mechanically ventilated and FiO<sub>2</sub> was adjusted based on previous PaO<sub>2</sub>. A rapid reduction in PaO<sub>2</sub> occurred at 12 hr – 18 hr [red], which was treated by increasing FiO<sub>2</sub> [blue]. However, there was a several hr delay in adjusting the FiO<sub>2</sub>.**

Closed loop FiO2 controllers: We have performed in vivo testing for both CLC-FiO2 [Impact 731 & Hamilton G5]. The specific goal of this initial testing was to determine:

- 1) Signal fidelity
- 2) Usability and data signals
- 3) Finally, can the CLC-FiO2 algorithm be used to develop SOS that predicts pulmonary injury
  - a. Need for LSI
  - b. Variations that could be normal and no LSI needed

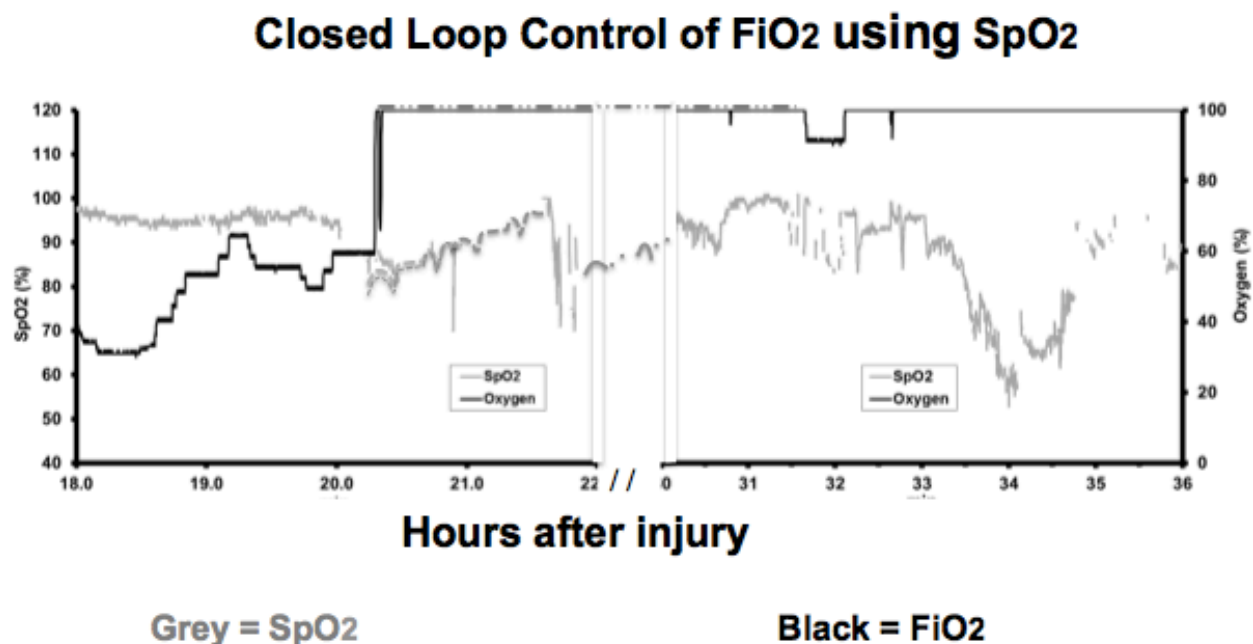


**Figure 26. Impact 731: CLC-FiO2 controller with recorded signals for FiO2 and SpO2**

*Impact 731 CLC-FiO2*: The 731 underwent several engineering modifications to address communication issues. After the communication protocol was repaired, we tested the device. We were unable to engage the CLC-FiO2 [despite adequate pulse oximetry] in one experiment. Therefore, no data was acquired. The CLC-FiO2 was activated in second experiment [7 hour study or 420 min]. Figure 26 shows time course and CLC-FiO2 activation for the 731. Initially, the FiO2 was set to 0.21. The pulse oximeter reading was initially 99%. The CLC-FiO2 controller was activated [a display showing a rotating circle was indicated on the 731]. During the first 20 min, small reduction in SpO2 occurred, however, did not reach the threshold of 92%. Approximately 40 min into testing, the pulse oximeter had a poor reading – the FiO2 immediately climbed to 1.0; despite SpO2 >95%. Thereafter, the FiO2 was slowly and incrementally reduced. A rapid reduction to FiO2 of 0.4 occurred at 60 min. Similarly, at 230 min, a poor pulse ox reading occurred and the CLC-FiO2 increased to 0.6 with decrements over several hours. SpO2 did not truly fall below 93%. Aberrant, signals occurred every 6-20 min [FiO2 readings of 0.8]. These show as spikes on the FiO2 recording, which likely can be filtered. On the other hand, rapid increases despite normal SpO2 and ‘sluggish’ readjustment need software modifications.



*Hamilton G5 Intellivent's CLC-FiO2*: After performing similar in vivo testing [above], we shifted our efforts to use the Intellivent CLC-FiO2 to generate the SOS. The Intellivent CLC-FiO2 provides a more robust and stable signal. Thus, pulmonary treatment decisions [LSIs], which are outlined in DS protocol, will likely incorporate the Intellivent CLC-FiO2 algorithm responsiveness. Decisions such as when to institute positive pressure ventilation [PPV], adjust PPV {modes and amount of pressure}, PEEP and pulmonary toilet, will be based on the rate of change and level of FiO2. We have begun capturing data in sheep undergo burn and smoke injury as outlined in ACURO protocol. After placing and securing a Masimo pulse oximeter [as described] the Intellivent CLC-FiO2 is activated, which automatically adjusts FiO2 based on SpO2. Data are transcribed and ventilatory data from the Intellivent and hemodynamics are electronically recorded. Figure 27 shows SpO2 and FiO2 during a time when pulmonary function starts to deteriorate. At 18.5 hr, the CLC-FiO2 became active with an increasing need for FiO2, in order to keep SpO2 > 93%. The rate of increase for FiO2 was 20% over 1 hr. At 20.5 hr, SpO2 fell and the FiO2 increased to 1.0. Positive pressure ventilation [PPV] was initiated at this time. There were other periods of desaturations with maximal FiO2 [SpO2 <85%] @ 22 hr and @ 34 hr, which pulmonary toilet was performed and PEEP was added.



**Figure 27. Hamilton G5 Intellivent CLC-FiO2.** Spo2 and FiO2 recordings from 18hr – 36 hr with a time break between 22 hr/30hr. In this example, sheep initially ventilated via trach tube connected to the G5 Intellivent spontaneously with minimal pressure support [5 cmH2O]. At 20.5 hr PPV was begun. Pulmonary toilet [bag + suction] interventions were performed at 22hr and 34 hr.

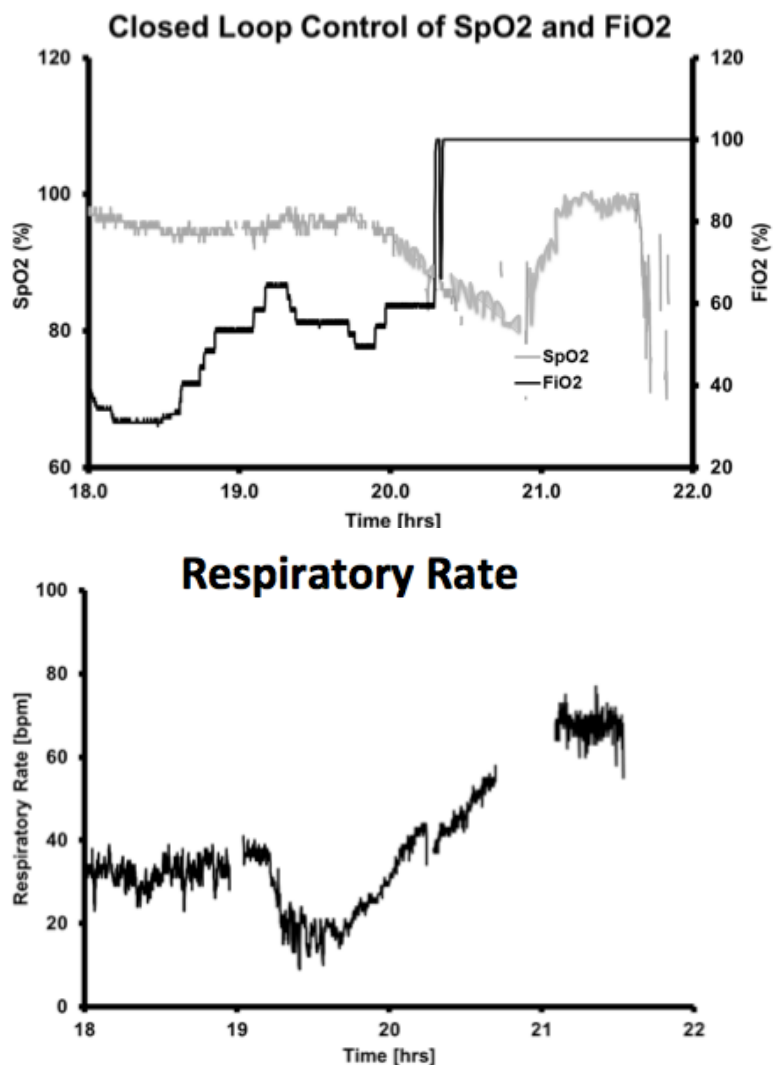


Figure 28. Demonstrates the G5 Intellivent CLC-FiO2 display of SpO2 and FiO2 and respiratory rate captured at the same time. The FiO2 preceded clinical tachypnea by at least 1hr.

#### Early warning of respiratory distress:

The use of CLC-FiO2 to detect pending respiratory distress is evident and potentially a **powerful early warning signal that even precedes clinical signs**. Figure 28 demonstrates the FiO2 and SpO2 from 18-22 hr and the respiratory rate digitally captured at the same time using the G5 Intellivent. In this 4 hr zoom-in window [figure 27], FiO2 began increasing at 18.5 hr. Over a one-hour time period [from 18.5-19.5hr] the CLC-FiO2 algorithm generated a large increase in FiO2 to maintain SpO2, which represents a two-fold increase in oxygen requirements [0.3 to 0.6], thereafter a plateau occurred for approximately one hour followed by another substantial increase in FiO2 due to developing hypoxemia. Interestingly, respiratory rate did not increase until hypoxemia developed. Hemodynamics and other vent parameters were not changed. This demonstrates that CLC-FiO2 predicts respiratory distress prior to clinical signs. The FiO2 increase has been observed in all sheep [n=3] that have pulmonary deterioration. Figure 28 is an example of hi – resolution data from an animal.

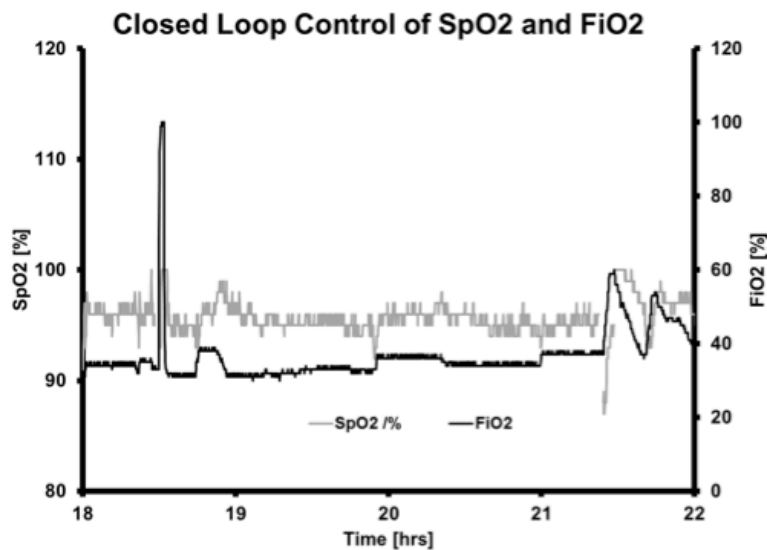


Figure 29. CLC-FiO2 demonstrating small transient oscillations

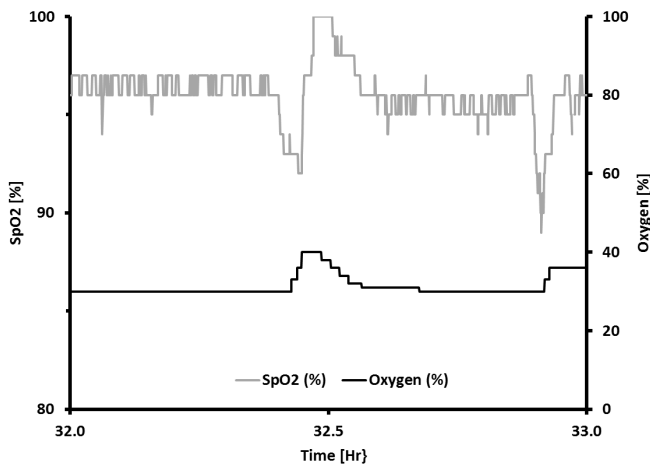


Figure 30. Demonstrates the rapid response of G5 Intellivent CLC-FiO2. This is 1 hr display window for SpO2 and FiO2.

Recognition of non-respiratory distress: Data recorded from another experiment [different animal at a similar time period], demonstrates normal changes that do not suggest respiratory distress. Whether these are normal patterns or oscillations, it is important that LSI's or treatments do not become initiated [negative predictive value]. Figure 29. Shows hi-resolution data capture from the CLC-FiO2 over a 4 hr period [and a smaller 1 hr zoom]. FiO2 increases are transient and are not associated with other physiologic changes. The amplitude and duration of the response is critical to make treatment decisions. The figure also demonstrates the precise reactivity of the CLC-FiO2 algorithm— for example, decreases in SpO2 yield a rapid response in FiO2. When FiO2 increases, there is strong physiologic feedback in SpO2. **Thus, FiO2 acts as a provocative challenge to the lung to test the responsiveness – if SpO2 increases, then lung function is relatively intact, on the other hand, if SpO2 does not increase, then lung injury is likely present.** There are, however, some limitations with the G5 Intellivent. For example, the lower

limit for FiO2 is 0.3 and each spontaneous breathing trial can only be programmed for 6hr. Both of these are software changes. Hamilton has provided the PI assurance that these will be extended.

**Summary:** We continue to collect data generated CLC-FiO<sub>2</sub> algorithm, respiratory parameters, hemodynamics and fluid balance in hi-resolution. Blood analytes are also recorded. Together, these will provide input signals to develop the SOS. The PI will meet with Dr. Jose Salinas during this reporting period [October 14-16]. Dr. Salinas will use the data and help construct a user-friendly SOS platform that displays the data in real-time and provides a technology for identifying respiratory distress.

**Key Accomplishments:**

1. Regulatory approval of ACURO 12339090.01, QTR 1: 12-20-2012
2. Regulatory approval of ACURO 12339090.02, QTR1: 12-20-2012
3. Hardware acquisition and testing for objectives, QTR1-3: 01-03-2013 thru 06-30-2013
4. Task 1 –Collect oxygenation data (FiO2 and SpO2) and other data in sheep after moderate and severe inhalation injury – near complete and have incorporated data into SOS support algorithm, QTR 3: 04-01 to 06-30-2013
5. Task 5 – Collect FiO2, SpO2, ventilatory parameters, CO2 production, hemodynamics and indices of perfusion during hypovolemia and pulmonary injury – data incorporation into SOS algorithm, QTR 3: 04-01 to 06-30-2013
6. Task 2 – Develop SOS algorithm and prototype for pulmonary injury: now evaluating two CLC-FiO2 system's [Hamilton and impact – see below issues] QTR 3: 04-01 to 06-30-2013
7. Task 3 – Task #3: Test SOS vs Standard of Care (SOC) for determining LSI after moderate and severe inhalation injury. Adapted decision support aim QTR 3&4: 04-01 to 09-30-2013
8. Submission new IACUC protocol, QTR 4: 09-23-2013
9. Task 2 – Develop SOS algorithm and prototype for pulmonary injury: now evaluating two CLC-FiO2 system's [Hamilton and impact –below issues] QTR 3&4: 04-01 to 09-30-2013

**Reportable Outcomes:**

We are still early in project and development.

**Inventions disclosed:**

none

**Conclusion:**

The implications of this project are that we are developing a technology/product that could provide a powerful early warning signal that precedes clinical signs of deterioration. Further, we continue to examine if close loop controllers can act as a provocative challenge to test the physiologic and pathologic responsiveness. To some extent, we are developing an algorithm within an algorithm.

**References and Appendices:**

none